DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/13/09 has been entered.

2. Claims 1-37, 77, 83-94, 97-108, 119, and 121-123 are all the pending claims for this application.

3. Claims 1-37, 77, 84-87, 93, 94, 97, 101-108 are withdrawn from examination.

4. Claims 118 and 120 were cancelled and Claim 121 was amended in the Response of 8/13/09.

5. Claims 83, 88-92, 98-100, 119 and 121-123 are all the pending claims under examination with targeting units for a ligand species of soluble CD40 ligand and the chemokines, RANTES and MIP-1α, and the species of antigenic units for an antigenic scFv.

6. This Office Action contains new grounds for objection and rejection.

Information Disclosure Statement

7. The IDS of 8/13/09 has been considered and entered. The examiner's initialed and signed copy of the 1449 is attached.

Withdrawal of Objections

Claim Objections

8. The objection to Claims 120 and 121 because they reference two sets of claims drawn to different features (MPEP 608.01(n)) is moot for cancelled Claim 120.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Enablement

9. The rejection of Claims 118 (and 120) under 35 U.S.C. 112, first paragraph, for lack of enablement is moot and withdrawn in view of the cancelled claims.

Applicants comments on p. 14 of the Response of 8/13/09 are acknowledged.

Claim Rejections - 35 USC § 102

10. The rejection of Claims 83, 88-92, 98-100, 119 and 121-123 are rejected under 35 U.S.C. 102(e) as being anticipated by Herman (US 20050069549; published March 31, 2005; filed Jan 14, 2003; cited in the PTO 892 form of 11/7/06) is withdrawn.

Applicants allegations on pp. 14-19 of the Response of 8/13/09 have been considered and are found persuasive. Applicants allege "Anticipation requires disclosure of all the claimed features as arranged in the claim - there must be an instance, description, or embodiment that expressly accounts for all aspects of Applicants' claim as arranged in the claim."

New Grounds for Objection

Claim Objections

11. Claim 122 is objected to because of the following informalities: Claim 122 depends from cancelled Claim 120. Appropriate correction is required.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 83, 88-92, 98-100, 119 and 121-123 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Herman (US 20050069549; published March 31, 2005; filed Jan 14, 2003; cited in the PTO 892 form of 11/7/06) in view of Slavin-Chiorini et al. (Int. J. Can. 53:97-103 (1993)).

Claims 83, 88-92, 98-100, 119 and 121-123 are interpreted as being drawn to an isolated nucleic acid encoding a monomer unit of a recombinant antibody-based dimeric molecule, said nucleic acid encoding an antigenic unit, a dimerization motif and a targeting unit operably connected to encode said monomer unit, and wherein said antibody-based dimeric molecule comprises two of said monomer units connected through said dimerization motif, said dimerization motif comprising an Ig hinge region and a Cy3 domain of each monomer unit, wherein each Ig hinge region contributes to dimerization via disulfide bridging to the other Ig hinge region and each Cy3 domain contributes to dimerization via hydrophobic interactions to the other Cy3 domain, and wherein each of said monomer unit comprises a targeting unit for an antigen presenting cell and an antigenic unit, wherein said targeting unit and said antigenic unit in the monomer unit are separated by said dimerization motif and wherein said monomer units each lack a CH2 domain (Claim 83), wherein at least one of said targeting unit is a ligand (Claim 88), and wherein said ligand is soluble CD40 ligand or a chemokine (Claim 89), wherein said ligand is a chemokine (Claim 90), wherein said chemokine is RANTES or Macrophage Inflammatory Protein 1 alpha (Claim 91), wherein said chemokine is MIP-Ia (Claim 92), wherein said targeting unit have the ability to target a chemokine receptor (Claim 98), wherein at least one of said antigenic unit is an antigenic scFv (Claim 99), wherein said antigenic scFv has VL and VH chains from a monoclonal Ig produced by myeloma or lymphoma (Claim 100).

Claim 119 is drawn to a vector comprising the nucleic acid according to claim 83.

Claim 121 is drawn to a composition comprising a nucleic acid according to claim

83 or a vector comprisinq the nucleic acid accordinq to claim 83, in combination with a physiologically acceptable diluent or carrier.

Claim 122 is drawn to a composition comprising a cell of the cell line according to claim 120, in combination with a physiologically acceptable diluent or carrier.

Claim 123 is drawn to a kit for preparation of a recombinant antibody- based molecule encoded by the nucleic acid according to claim 83, the kit comprising a nucleic acid according to claim 83.

The nucleic acid encoding a monomer comprising the (targeting unit – dimerization motif (Ig hinge *and* Cγ3)- antigenic unit) or (antigenic unit- dimerization motif (Ig hinge *and* Cγ3)- targeting unit) was prima facie obvious at the time of the invention over Herman and Slavin-Chiorini.

Herman discloses nucleic acids, vectors comprising nucleic acids and vector transfected cell lines encoding a multispecific ligand comprising at least two different binding specificities for different target ligands comprising any combination of one or more antibody fragments or recombinant reconstructions (scFvs) of antibodies including tetraspecific antibody formats and fusions of the antibody to other functional moieties (eg. toxins, cytokines, chemokines, streptavidin, adhesion molecules) [0107-0108], where the multispecific ligand comprises an Fc portion and an Ig hinge portion. An Fc portion may be a partial Fc portion (eg. minibody-CH3) [0069]. The amino acid composition (including length) of the hinge portion should provide means for linking two typically heavy chains, eg. through one or more disulfide bonds, leucine zipper, fos-jun, optionally a flexible hinge typical of an IgG1 or having one to several more disulfide

bonds eg. IgG3) [0116]. The binding characteristics of the multispecific ligand e.g., scfv, is that the target ligand is of sufficient affinity to effectively bind or remain bound without the other unit being available for simultaneous binding [0119]. An example of one monomer comprises a first ligand moiety which recognizes a first target ligand that is over-expressed on a disease associated entity (for example a diseased or disease-causing or mediating cell or infectious agent) and a second ligand binding moiety that recognizes a target ligand and wherein the first target ligand is characterized in that it does not lend itself to facilitating or permitting internalization of the second ligand binding moiety [0122].

Herman discloses the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety that binds to a ligand which effects binding to another immune cell, for example a T cell or APC. The multispecific ligand is a tetraspecific antibody or the first moiety binds to but is incapable of modulating the activity of an immune cell and the second moiety modulates the activity of the immune cell independently of the first moiety [0137].

Herman discloses a multispecific ligand which comprises a first ligand binding moiety which neutralizes a ligand eg. a natural ligand such as a chemokine and a second ligand binding moiety which binds to a cell marker associated with a cell [0138]. Examples of proteins which are targeted by multispecific ligand (targeting unit) include CD40 [0164], MIP-1 alpha and RANTES [0428]. Herman discloses a multispecific ligand comprising an anti-idiotype antibody (antigenic unit) so as to facilitate a desired immune response eg. vaccination type responses [0172, 0252]. For one embodiment, Herman

discloses a multispecific ligand containing an immunocytokine containing an anti-idiotypic antibody component and a cytokine component [0018]. Herman discloses nucleic acids, expression vectors and host cells expressing the vectors to produce a multispecific ligand [0241- 0298; 0314-0319]. Herman discloses a kit comprising one or more polynucleotides comprising one or more DNA sequences, where the DNA sequences encode one or more polypeptides which are sufficient to constitute a multispecific ligand as defined in any of the preceding paragraphs [0424]. Herman discloses the element of CH2 domain being optional and the element of CH3 domain being optional whereas Slavin-Chiorini discloses deleting the CH2 domain altogether and maintaining a CH3 constant domain for an Ig molecule.

Slavin-Chiorini discloses the long-felt need to obtain recombinant Ig molecules with rapid plasma clearance and little or no ability to elicit a HAMA response for use in diagnostic or therapeutic regimens, and that by deleting the CH2 domain of an intact Mab, the ordinary artisan could reasonably expect to obtain these results for murine and chimeric antibodies (p. 97, Col. 1, ¶1 and 3). The Ig molecule is shown in Figure 1 comprising a CH2 constant region deletion, an intact hinge region with a linker peptide bridging the CH1 and CH3 constant domains. Slavin-Chiorini discloses there is a reduction in disulfide bond formation between the heavy chains for the CH2 domain deletion, but that presence of the peptide linker may contribute to the stability of the Ig molecule. Slavin-Chiorini discloses that these alternative forms of Ig molecules demonstrate faster clearance rate, more rapid tumor targeting and lack of metabolic uptake in normal tissues which provide advantages over the full molecules.

The ordinary artisan would have been motivated and assured of success in having produced a nucleic acid encoding a monomer comprising the (targeting unit – dimerization motif (Ig hinge *and* Cγ3)- antigenic unit) or (antigenic unit- dimerization motif (Ig hinge *and* Cγ3)- targeting unit) based on the combined disclosures of Herman and Slavin-Chiorini. Herman teaches all of the elements for designing such a construct, for example, fusion proteins comprising a immunocytokine having an anti-idiotypic antibody component and a cytokine component fused therewith or conjugated thereto, or ligands including bispecific antibodies, antibody fusions/ conjugates eg. where the immune affecting antibody portion or other moiety is conjugated, fused etc. to an antibody or fragment that binds to an entity associated marker [0223]. Herman teaches making a "divalent immunoconjugate" by attaching therapeutic agents to a carbohydrate moiety and to a free sulfhydryl group [0338]. Accordingly, Herman teaches an example of a bispecific antibody comprising two dAb components comprising linked via a linker having at least part of a constant region for fusion for example to a toxin (eg. at least a partial hinge region, and preferably also at least a partial CH2 domain (optionally also at least a partial CH3 domain) [0345]. Herman requires the hinge region, does not necessarily require the CH2 domain although preferable, and may include the CH3 domain, which is considered to read on the constructs in view of all of the other elements taught (and discussed above) by Herman as possible combinations for constructs. The ordinary artisan would have been motivated to have deleted the CH2 domain entirely from the construct of Herman where it was well known according to Slavin-Chiorini at the time of the invention, that the CH2 domain contains many of the

effector functions for the constant region of an Ig and the sole N-linked glycosyaltion site in human Cγ1. Eliminating the CH2 domain would renders the Ig into a less complex molecule in terms of reduced immunogenicity, increased target specificity and rapid clearance from circulation. Maintaining the a linker and CH3 domain according to Slavin-Chiorini at the time of the invention would stabilize the expressed molecular complex with respect to binding (It is not a requirement that the Examiner establish that the cited art contains all the elements of the rejected claim, as the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR, 550 U.S. at 418.).

The ordinary artisan would have been assured of reasonably success in having produced the nucleic acid where each of the reference taught the reagents and steps for making recombinant Ig-like molecules with bi-specific binding properties, to maximize the stability of an expressed protein monomer in pairwise formation via a linker and CH3 domain, and to reduce non-specific biological effects for an Ig-like molecule by deleting the CH2 domain. For all of these reasons, the claims were prima facie obvious at the time of the invention.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Primary Examiner
Art Unit 1643